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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/790,662	03/01/2004	David J. Chaplin	18217-519 (OXI-19)	9569

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EXAMINER	
BETTON, TIMOTHY E	
ART UNIT	PAPER NUMBER
1617	
MAIL DATE	DELIVERY MODE
10/02/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/790,662	CHAPLIN ET AL.	
	Examiner	Art Unit	
	TIMOTHY E. BETTON	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-57* is/are pending in the application.

4a) Of the above claim(s) *17-33 and 43-56* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16,34-42 and 57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants Remarks filed 7 May 2008 has been acknowledged and duly made of record.

The essence of applicant arguments are drawn to issue that the lack of an explicit synthesis of ZSB-71 is the sole basis for the present rejection in the present application.

The current Remarks as disclosed contains embodiments drawn to the explanation of the use of *dozens of closely related compounds* at the exclusion of the ZSB-71 chemical compound which was specifically elected by applicant. It is unclear to the Examiner as to how *dozens of closely related compounds* may exemplify the same results as ZSB-71, a distinct compound. Though, properties and characteristics of the same may overlap with regard to the disclosed compounds, these compounds do not represent ZSB-71 in the scope of applicants' election and claimed invention. Accordingly, susceptibilities of the variable compounds may differ in view of synthesis and indicated use. The Remarks as filed are speculative with regard to ZSB-71. Applicants' operative embodiments drawn to ZSB-71 are absent in the same specification and unclear and vague in the Remarks as filed.

ZSB-71 is taught as a "Tubulin Binding Agent" shall refer to a ligand of tubulin or a compound capable of binding or tubulin monomers, tubulin heterodimers, or polymerized microtubules and interfering with the polymerization or depolymerization of microtubules. The exact nature of tubulin binding site interactions remains largely unknown, and they definitely vary between each class of Tubulin Binding Agent. Photoaffinity labeling and other binding site elucidation techniques have identified three key binding sites: 1) the Colchicine site (Floyd et al, Biochemistry, 1989; Staretz et al, J. Org. Chem., 1993; Williams et al, J. Biol. Chem., 1985; Wolffet al, Proc. Natl. Acad. Sci. U.S.A., 1991), 2) the Vinca Alkaloid site (Safa et al, Biochemistry, 1987), and 3) a site on the polymerized microtubule to which taxol binds (Rao et al, J. Natl. Cancer Inst., 1992; Lin et al, Biochemistry, 1989; Sawada et al, Bioconjugate Chem, 1993; Sawada et al, Biochem. Biophys. Res. Commun., 1991; Sawada et al, Biochem. Pharmacol., 1993). Tubulin binding agents contemplated by the present invention contain at least one aryl moiety where a catechol or quinone structure can be introduced in order to generate a "Dual activity" agent (specfn. pg 15, 1st paragraph, lines 1-14).

The limitation of the claims drawn to a specific structure, limitations drawn to treating cancer, and assessing which quinone or catechol will possess the data necessary will be further determined. In the absence of findings drawn to a use for ZSB-71, the burden is upon the applicant to exemplify which compound is enabled if the ZSB-71 is not deemed the representative compound in light of current invention.

Applicants' understanding is that this compound election is for searching purposes only and upon a finding of allowability of the elected compound, the remaining compounds will also be searched.

However, while the elected species is free of the prior art, the issue drawn to enablement still exists for the same elected species. Thus, the species is not allowable and a search to other related species as disclosed will not be extended.

Examples in the specification which seem to indicate a representative agent for treatment is not disclosed in the scope of the current invention. For instance, applicants attention is directed to the specification, (pg. 31), which discloses Example I describing the synthesis of CA-1 ortho-quinone. CA-1 ortho-quinone is the only compound disclosed in the same specification to be used to treat tumor blood flow (please see pages 73-75).

However, the limitation attributed to claim 1 discloses a composition comprising a catechol or quinone or derivative thereof , ***provided that the composition is not combretastatin A-1 or a salt, ester, or prodrug thereof.***

ZSB species are disclosed in the specification with values drawn to catechol properties (pg. 68) and peroxidase-mediated activation of catechols (pg. 72), but do not suggest or support the use of any specific ZSB species, let alone ZSB-71 in a method of treating as claimed.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-16, 34-42, and 57 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for some compounds such as drawn specifically to the treatment for certain catechol-containing compounds and their prodrugs, which selectively reduce blood flow to a tumor region, does not reasonably provide enablement for ZSB-71 for the selective reduction of blood flow to a tumor region . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in Exparte Forman, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in In re Wands, 8 USPQ2d 1400 at 1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include:

1) the quantity of experimentation necessary
2) the amount of direction or guidance provided
3) the presence or absence of working examples
4) the nature of the invention
5) the state of the art
6) the relative skill of those in the art
7) the predictability of the art and
8) the breadth of the claims

Nature of the Invention, Breadth of the claims and the State of the art

The nature of the invention is drawn to a composition which selectively reduces blood flow to a tumor region and forms a reactive oxygen species *in vivo*. Breadth of the claims are drawn to the said composition which comprises an anticancer agent having a quinone, quinone prodrug, catechol or catechol prodrug moiety, provided that said composition is not combretastatin A-1 or a salt, ester or prodrug thereof. Claim 2 depends from claim 1 and is drawn to said moiety in the ortho position. Claim 3 depends from claim 1 and is drawn to said anticancer agent as a tubulin binding agent.

The state of the art is taught in Wartchow et al. (USPGPUB) which discloses embodiments replete with Targeted therapeutic agents, comprising a linking carrier, a therapeutic entity associated with the linking carrier, and at least one targeting entity are provided, **as well as methods for their preparation and use** (abstract only). Wartchow et al. does not teach ZSB-71, but it teaches categories and classes of antineoplastic agents which read on each and every limitation drawn to claim 3.

ZSB-71 is indicated as a tubulin binding agent according to current invention but presents none of the embodiments in any representative form in order to determine a clear scope of enablement drawn to use.

The Amount of direction or guidance provided and Working models

The elected compound ZSB-71 is cited in the specification separately on pages 64, 68, and 72, but the amount of direction and guidance with regard to the claimed subject matter

directed to the elected compound is deficient. Disclosure drawn to catechols dissolved in DMSO is drawn to ZSB-71 as one of a number of cathecols. However, actual description, explanation, and/or reasoning as to how ZSB-71 is used in order to arrive at the treatment limitations of the claims are completely silent. Based on the lack of teaching, the assertion by Examiner is that ZSB-71 is not enabled in view of the scope of claimed invention.

Accordingly, the applicant cites: Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, numerous equivalents to the specific procedures described herein. Such equivalents are considered to be within the scope of the invention and are covered by the following claims. Various substitutions, alterations, and modifications may be made to the invention without departing from the spirit and scope of the invention as defined by the claims. Other aspects, advantages, and modifications are within the scope of the invention. The contents of all references, issued patents, and published patent applications cited throughout this application are hereby incorporated by reference. The appropriate components, processes, and methods of those patents, applications and other documents may be selected for the invention and embodiments thereof (page 75, 2nd full paragraph).

However, the scope of invention of compounds encompassed within the claims cannot be adequately assessed or determined based on applicants' said disclosure or the examples embodied therein.

Predictability and Quantity of experimentation necessary

Chawla, S., Effect of Deoxyarbutin and its second-generation derivatives on melanocyte viability and function, Division of Research and Advanced Studies of the University of Cincinnati (2006), printed pages 1-216, especially page 80) teach that **[t]he catechol structure, with two hydroxyl (OH) groups at the ortho positions** (which reads generally on the elected compound), may behave as a chelator to the copper ions of tyrosinase [8]. **However, the rapid oxidation of catechols generates reactive quinones that can irritate the skin.** Therefore, phenolic compounds were considered potential inhibitors due to their ability to tightly bind tyrosinase and resist oxidation. **Substitution with electron withdrawing, hydrophobic and less bulky groups at the para position of phenol increases binding to tyrosinase and decreases the potential for oxidation, leading to effective inhibition [29]. These hydrophobic groups more efficiently interact with the hydrophobic protein pocket surrounding the binuclear copper active site [30-32].** deoxyArbutin and its second derivatives are structurally advantageous tyrosinase inhibitors. dA contains a pyran ring as the fourth substituent group on the phenol and an acetyl group in its molecular structure that confers a tight binding capacity and resistance to oxidation respectively [28]. These properties putatively account for dA's relative reduction in cytotoxicity compared to HQ. Furan in deoxyFuran and pyran in dA, tdA and fdA react to give substitution products. This tendency to favor substitution rather than addition suggests that the parent unsaturated ring system has exceptional stability (page 80, lines 5-21).

The disclosure above cites unpredictability of the elected compound based on the ortho-positioning and/or orientation as opposed to para- positioning and/or orientation. The quantity

of experimentation necessary as disclosed in Smita is replete with sufficient explanation, description and reasoning drawn to the inventive objective of claimed invention (please see pages 60, l. 12; 64, l. 4; 65, l. 9; 116, l. 14,139, l. 17).

Thus unpredictability in view of the scope of the claimed invention is high. The quantity of experimentation necessary would be undue because of the absence of embodiments drawn to a method process of use in a human patient in need of such treatment. A method of administration in the claims is not established. A target population in the claims is not sufficiently identified. As a result, there is nothing in the current invention which distinguishes ZSB-71 as being predictable in view of treatment for the disease as claimed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Timothy E. Betton whose telephone number is (571) 272-9922. The examiner can normally be reached on Monday-Friday 8:30a - 5:00p. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/James O. Wilson/
Supervisory Patent Examiner, Art Unit 1624
TEB